




## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification</b> <sup>6</sup> : <b>C07C 405/00, A61K 31/557</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 98/21180</b> <b>(43) International Publication Date:</b> 22 May 1998 (22.05.98)
<b>(21) International Application Number:</b> PCT/US96/17901 <b>(22) International Filing Date:</b> 12 November 1996 (12.11.96)  <b>(71) Applicant (for all designated States except US):</b> ALCON LABORATORIES, INC. [US/US]; 6201 South Freeway, Fort Worth, TX 76134-2099 (US).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> ZINKE, Paul, W. [US/US]; 4129 Willow Way Road, Fort Worth, TX 76133 (US). BISHOP, John, E. [US/US]; 878 Townsend Road, Groton, MA 01450 (US). DEAN, Thomas, R. [US/US]; 101 Meadow View Court, Weatherford, TX 76087 (US). HELLBERG, Mark, R. [US/US]; 5211 Override Drive, Arlington, TX 76107 (US).  <b>(74) Agents:</b> COPELAND, Barry, L. et al.; Alcon Laboratories, Inc., Patent Dept., Q-148, 6201 South Freeway, Fort Worth, TX 76134-2099 (US).		<b>(81) Designated States:</b> AU, CA, CN, JP, MX, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>With international search report.</i>  
<b>(54) Title:</b> CONFORMATIONALLY RIGID ARYL- OR HETEROARYL PROSTAGLANDINS FOR USE IN GLAUCOMA THERAPY		
<b>(57) Abstract</b>  Conformationally rigid aryl prostaglandins are useful in the treatment of glaucoma and ocular hypertension. Also disclosed are ophthalmic, pharmaceutical compositions comprising said prostaglandins.		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

5 CONFORMATIONALLY RIGID ARYL- OR HETEROARYL PROSTAGLANDINS FOR USE IN GLAUCOMA THERAPY

10 Background of the Invention

The present invention relates to the use of prostaglandins and prostaglandin analogues for the treatment of glaucoma and ocular hypertension. As used herein, the  
15 terms "prostaglandin" and "PG" shall refer to prostaglandins and derivatives and analogues thereof, except as otherwise indicated by context.

Naturally-occurring prostaglandins, especially prostaglandins of the F series (such as PGF<sub>2</sub> $\alpha$  and the E series (such as PGE<sub>2</sub>), are known to lower intraocular pressure (IOP)  
20 after topical ocular instillation, but can cause conjunctival hyperemia and/or edema as well as inflammation. Many synthetic prostaglandins have been observed to lower intraocular pressure, but most such compounds also produce the aforementioned side effects which significantly limit their clinical utility.

25 Various attempts have been made to overcome these well-known side-effects. Some have synthesized derivatives of naturally-occurring prostaglandins in an attempt to design out selectively the side effects while maintaining the IOP-lowering effect. See, e.g., Stjernschantz et al. (U.S. 5,422,368 and 5,321,128), Woodward et al. (U.S. 5,093,329), Chan et al. (WO 92/08465 and U.S. 5,446,041). Others, including Ueno et al.  
30 (EP 330 511 A2) and Wheeler (EP 435 682 A2) have tried complexing prostaglandins with various cyclodextrins.

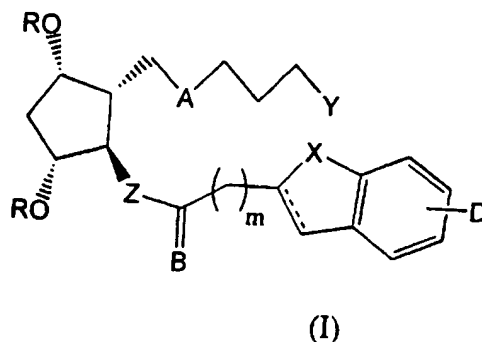
### Summary of the Invention

It has now been unexpectedly discovered that certain conformationally rigid analogues of PGF<sub>2</sub> $\alpha$  will lower or control IOP with no or significantly reduced side effects of conjunctival hyperemia and/or edema. An agent which exhibits comparable efficacy, but with reduced side effects when compared to other agents, is said to have an improved therapeutic profile.

While bound by no theories, it is believed that increased conformational rigidity resulting from the presence of a bicyclic ring at the terminus of the omega chain of the prostaglandins of the present invention allows increased discrimination amongst the various PG receptors, which, in turn, allows a higher separation of desirable and undesirable activities, and therefore an improved therapeutic profile.

### Detailed Description of the Invention

The conformationally rigid aryl prostaglandins which are useful in the compositions of the present invention have the general formula (I):



wherein:

$Y = C(O)NR_1R_2$ ,  $CH_2OR_3$ ,  $CH_2NR_1R_2$ ,  $CO_2R_1$ ,  $CO_2M$ , where M is a cationic salt moiety;

$R_1$ ,  $R_2$  (same or different) = H,  $C_1$ - $C_6$  alkyl or alkenyl, or  $C_3$ - $C_6$  cycloalkyl;

5  $R$ ,  $R_3$  (same or different) =  $C(O)R_4$ , or H, where  $R_4$  =  $C_1$ - $C_6$  alkyl or alkenyl, or

$C_3$ - $C_6$  cycloalkyl;

$A = CH_2CH_2$ , *cis* or *trans*  $CH=CH$ , or  $C\equiv C$ ;

10  $Z = CH_2CH_2$ , *trans*  $CH=CH$ ;

$X = O$ ,  $S(O)_n$ ,  $(CH_2)_n$ , or  $CH_2O$ , where  $n = 0, 1$ , or  $2$ ;

$B = H$  and  $OH$  in either configuration, or a double bonded  $O$ ;

$D = R_1$ ,  $OR_1$ , halogen,  $S(O)_nR_4$ ,  $NO_2$ ,  $NR_1R_2$ , or  $CF_3$ , where  $n = 0, 1$ , or  $2$ , and  $R_1$ ,  $R_2$ , and  $R_4$  are as defined above; and

15  $m = 0, 1$ , or  $2$ .

Most preferred compounds include:

II. (5*Z*, 13*E*)-(9*S*, 11*R*, 15*S*)-15-(2-indanyl)-9, 11, 15-trihydroxy-16, 17, 18, 19, 20-  
20 pentanor-5, 13-prostadienoic acid isopropyl ester.

III. (5*Z*)-(9*S*, 11*R*, 15*R*)-15-(2-indanyl)-9, 11, 15-trihydroxy-16, 17, 18, 19, 20-  
pentanor-5-prostenoic acid isopropyl ester.

25 IV. (5*Z*, 13*E*)-(9*S*, 11*R*, 15*S*)-15-(2*R*-(1,2,3,4-tetrahydronaphthyl))-trihydroxy-16, 17,  
18, 19, 20-pentanor-5, 13-prostadienoic acid isopropyl ester.

V. (5*Z*, 13*E*)-(9*S*, 11*R*, 15*S*)-15-(2*S*-(1,2,3,4-tetrahydronaphthyl))-9, 11, 15-  
trihydroxy-16, 17, 18, 19, 20-pentanor-5, 13-prostadienoic acid isopropyl ester.

- VI. (5Z, 13E)-(9S, 11R, 15R)-15-(2-benzo[b]furyl)-9, 11, 15-trihydroxy-16, 17, 18, 19, 20-pentanoic acid isopropyl ester.
- VII. (5Z, 13E)-(9S, 11R, 15R)-15-(2R-(2,3-dihydrobenzo[b]furyl)-9, 11, 15-trihydroxy-  
5 16, 17, 18, 19, 20-pentanoic acid isopropyl ester.
- VIII. (5Z, 13E)-(9S, 11R, 15R)-15-(2S-(2,3-dihydrobenzo[b]furyl)-9, 11, 15-trihydroxy-  
16, 17, 18, 19, 20-pentanoic acid isopropyl ester.
- IX. (5Z, 13E)-(9R, 11R, 15R)-15-(2R-[3,4-dihydro-2H-benzo[1,2-b]pyran-2-yl)-9, 11, 15-trihydroxy-16, 17, 18, 19, 20-pentanoic acid isopropyl ester.
- X. (5Z, 13E)-(9S, 11R, 15R)-15-(2S-3,4-dihydro-2H-benzo[1,2-b]pyran-2-yl)-9, 11, 15-trihydroxy-16, 17, 18, 19, 20-pentanoic acid isopropyl ester.

15 Some of the above-mentioned prostaglandins are disclosed in U.S. Patent No. 4,152,527 (Hess et al.) issued on May 1, 1979, and in Hyashi, M., et al., *J. Med. Chem.* 23:519 (1980). To the extent that U.S. Patent No. 4,152,527 discloses the synthesis of the prostaglandins of the present invention, that patent is incorporated by reference herein.

20 The compounds of formula (I) wherein  $Z = CH_2CH_2$  (and the other constituents are as defined above) are believed to be novel. The preferred novel  $PGF_{2\alpha}$  derivatives include those novel compounds of formula (I) wherein:  $X = CH_2$  and  $A = CH_2CH_2$ , or *cis*  $CH=CH$ .

25 The compounds of formula (I) can be prepared by generally employing the methods disclosed in the foregoing references or in the following example. The following synthesis is representative of those which may be used to prepare compounds of the present invention. Those skilled in the art will appreciate the modifications to the synthesis of Example 1 necessary to yield such compounds.

In the foregoing illustrations, as well as those provided hereinafter, a hatched line, as used e.g. at carbon 9, indicates the  $\alpha$  configuration. A solid triangular line indicates the  $\beta$  configuration. Dashed lines on bonds indicate a single or double bond. Two solid lines between carbons indicate a double bond of the specified configuration.

5

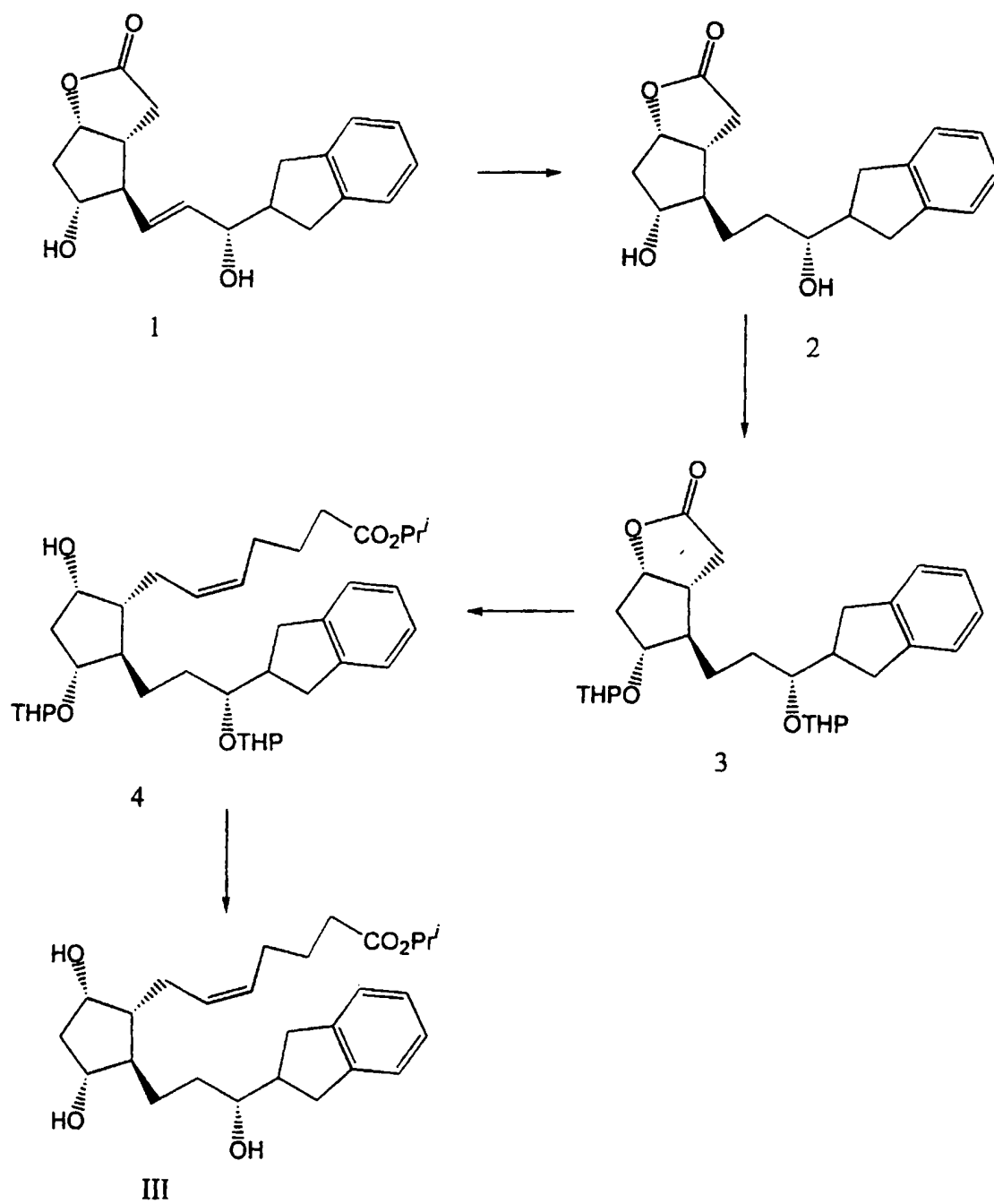
In the Example 1 which follows, the following standard abbreviations are used:  
g = grams (mg = milligrams); mol = moles (mmol = millimoles); mL = milliliters;  
mm Hg = millimeters of mercury; mp = melting point; bp = boiling point; h = hours; and  
min = minutes. In addition, "NMR" refers to nuclear magnetic resonance spectroscopy  
and "MS" refers to mass spectrometry.

10

### EXAMPLE 1

Synthesis of (5Z)-(9S, 11R, 15R)-15-(2-indanyl)-9, 11, 15-trihydroxy-16,  
17, 18, 19, 20-pentanoic acid isopropyl ester (III).

15





A: [3aR, 4R(1E, 3R), 5R, 6aS]-4-[3-hydroxy-3-(2-indanyl)propyl]-5-hydroxy-hexahydro-2H-cyclopenta[b]furan-2-one (2).

A solution of olefin 1 (0.7g, 2.2 mmol) [synthesis described in: *J. Med. Chem.* 26:328 (1983)] in 10 mL of a 1:1 v:v mixture of methanol:ethyl acetate was hydrogenated in the presence of 10% Pd/C (50mg) at 40 psi in a Parr hydrogenation apparatus for 1h. The mixture was filtered through Celite 521 and concentrated to afford 2, which was used in the next step without further purification.

B: [3aR, 4R(1E, 3R), 5R, 6aS]-4-[3-(2-indanyl)-3-(tetrahydropyran-2-yloxy)propyl]-5-(tetrahydropyran-2-yloxy)-hexahydro-2H-cyclopenta[b]furan-2-one (3).

Compound 2 from above was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (30mL) and the mixture was cooled to 0°C. 3,4-Dihydro-2H-pyran was added (0.42 g, 5.0 mmol), followed by *p*-toluenesulfonic acid monohydrate (50mg, 0.2 mmol). The solution was stirred at room temperature for 2h, poured into saturated aqueous NaHCO<sub>3</sub>, and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The solution was dried over MgSO<sub>4</sub>, filtered, and concentrated, and the residue was chromatographed on Silica Gel 60 (230-400 mesh ASTM) to afford 0.4 g (36%) of 3 as a viscous oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.2 (m, 4 H), 5.0 (m, 1 H), 4.7 (m, 2H), 4.1 (m, 1H), 3.9-3.6 (m, 3H), 3.5 (m, 2H), 3.2-2.5 (bm, 8H), 2.4-2.0 (m, 1H), 1.8-1.3(m, 18H).

C: (5Z)-(9S, 11R, 15R)-11,15-bis(tetrahydropyran-2-yloxy)-9-hydroxy-15-(2-indanyl)-16,17,18,19,20-pentanor-5-prostenoic acid isopropyl ester (4).

To a -78°C solution of lactone 3 (0.4 g, 0.8 mmol) in toluene (10 mL) was added a 1.5 M solution of DIBAL-H in hexane (1 mL, 1 mmol). After stirring for 2 h at 0°C, isopropanol (0.2 mL) was added, the mixture was poured into a solution of sodium potassium tartrate, extracted with ethyl acetate (2 x 50 mL), dried (MgSO<sub>4</sub>), and concentrated to afford 0.21 g (52%) of crude lactol.

To a solution of (4-carboxybutyl)triphenylphosphonium bromide (0.13 g, 0.3 mmol) in DMSO (6 mL) was added a DMSO solution of sodium methylsulfinylmethide (0.6 mmol, 0.2 M in DMSO). To the mixture was added dropwise a solution of the above lactol (0.15 g, 0.3 mmol) in DMSO (3 mL). The solution was stirred for 16 h at 50°C,  
5 cooled to room temperature, and quenched by the addition of 10% aqueous citric acid to pH 5.5. The mixture was extracted with ethyl acetate, dried (MgSO<sub>4</sub>), filtered, and concentrated.

The crude acid (0.2g, 0.4 mmol) was dissolved in acetone (20 mL) and treated  
10 with DBU (0.15 g, 1.0 mmol) and 2-iodopropane (0.17g, 1.0 mmol) for 16h at 23°C, then poured into water and extracted with ether (2 x 50 mL). The residue was purified by flash chromatography on Silica Gel 60 (230-400 mesh ASTM) with 3:1 hexanes: ethyl acetate to furnish 0.175 g (71%) of the isopropyl ester 4. PMR (CDCl<sub>3</sub>) δ 7.13 (m, 4H), 5.4 (m, 2H), 4.7 (m, 2H), 5.0 (hept, J = 6.3 Hz, 1H), 4.8-4.6 (m, 2H), 4.1-3.6 (m, 5H), 3.5(m,  
15 2H), 3.1-2.7 (6m, 4H), 2.3 (t, 2H), 2.1 (m, 2H), 1.9-1.2 (bm, 29H), 1.2 (d, J = 6.3 Hz, 6H).

D: (5Z)-(9S,11R,15R)-15-(2-indanyl)-9, 11, 15-trihydroxy-16, 17, 18, 19, 20-pentanoic-5-  
20 prostenoic acid isopropyl ester (III).

The isopropyl ester, 4, (0.10 g, 0.16 mmol) was dissolved in acetic acid/THF/H<sub>2</sub>O (4:2:1) and stirred at 50°C for 30 min., then stirred at 23°C for 16h. The solution was  
25 poured into a saturated aqueous NaHCO<sub>3</sub> solution and extracted with ethyl acetate (1 x 50 mL) and ether (1 x 50 mL) sequentially. The combined organic extracts were washed with water, dried over MgSO<sub>4</sub>, filtered and concentrated *in-vacuo*. The residue was purified by flash chromatography on Silica Gel 60 (230-400 mesh ASTM) with a 3:1 mixture of ethyl acetate : hexanes as eluent. This yielded 0.017 g (20%) of III as a pale  
30 yellow oil. PMR (CDCl<sub>3</sub>) δ 7.1 (m, 4H) 5.4 (m, 2H), 4.9 (hept, J = 6.3 Hz, 1H), 4.2 (m, 1H), 3.9 (m, 1H), 3.6 (m, 1H), 3.1-2.6 (bm, 5H), 2.3-1.9 (bm, 10H), 1.8-1.3 (bm,

10H), 1.1 (d, J = 6.3 Hz, 6H), CMR (CDCl<sub>3</sub>) δ 173.46, 143.01, 142.85, 129.63, 129.33, 126.24, 126.91, 124.47, 124.34, 78.81, 75.26, 74.73, 67.66, 52.91, 52.00, 46.08, 42.59, 35.85, 35.39, 34.25, 34.04, 29.77, 26.90, 26.64, 24.93, 21.84.

5       The conformationally rigid prostaglandins of the present invention may be formulated in various pharmaceutical compositions for administering to humans and other mammals as a treatment of glaucoma or ocular hypertension. As used herein, the term “pharmaceutically effective amount” refers to that amount of a compound of the present invention which lowers IOP when administered to a patient, especially a mammal. The preferred route of administration is topical. The compounds of the present invention may be administered as solutions, suspensions, or emulsions (dispersions) in an ophthalmically acceptable vehicle. As used herein, the term “ophthalmically acceptable vehicle” refers to any substance or combination of substances which are effectively non-reactive with the compounds and suitable for administration to a patient. Stabilizers and/or solubilizers are not considered to be reactive substances. Preferred are aqueous vehicles suitable for topical application to the patient's eyes.

      The compounds of the present invention are preferably administered topically. The dosage range is generally between about 0.01 and about 1000 micrograms per eye (μg/eye) and is preferably between about 0.1 and 100 μg/eye. In forming compositions for topical administration, the compounds of the present invention are generally formulated as between about 0.001 to about 1.0 percent by weight (wt%) solutions in water at a pH between about 4.5 to 8.0 and preferably between about 7.0 and 7.5. The compounds are preferably formulated as between about 0.0001 to about 0.1 wt% and, most preferably, between about 0.001 and about 0.02 wt%. While the precise regimen is left to the discretion of the clinician, it is recommended that the resulting solution be topically applied by placing one drop in each eye one or two times a day.

      Other ingredients which may be desirable to use in the ophthalmic preparations of the present invention include preservatives, co-solvents and viscosity building agents.

Antimicrobial Preservatives:

Ophthalmic products are typically packaged in multidose form. Preservatives are thus required to prevent microbial contamination during use. Suitable preservatives include: benzalkonium chloride, thimerosal, chlorobutanol, methyl paraben, propyl paraben, phenylethyl alcohol, edetate disodium, sorbic acid, Onamer M, or other agents known to those skilled in the art. Such preservatives are typically employed at a level between about 0.001% and about 1.0% by weight.

Co-Solvents:

Prostaglandins, and particularly ester derivatives, typically have limited solubility in water and therefore may require a surfactant or other appropriate co-solvent in the composition. Such co-solvents include: Polysorbate 20, 60 and 80; Pluronic F-68, F-84 and P-103; cyclodextrin; CREMOPHORE® EL (polyoxyl 35 castor oil); or other agents known to those skilled in the art. Such co-solvents are typically employed at a level between about 0.01% and about 2% by weight.

Viscosity Agents:

Viscosity greater than that of simple aqueous solutions may be desirable to increase ocular absorption of the active compound, to decrease variability in dispensing the formulations, to decrease physical separation of components of a suspension or emulsion of formulation and/or otherwise to improve the ophthalmic formulation. Such viscosity building agents include, for example, polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxy propyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxy propyl cellulose, chondroitin sulfate and salts thereof, hyaluronic acid and salts thereof, combinations of the foregoing, and other agents known to those skilled

in the art. Such agents are typically employed at a level between about 0.01% and about 2% by weight.

The following examples are representative pharmaceutical compositions of the  
5 invention for topical use in lowering of intraocular pressure.

EXAMPLE 2

The following formulations A-E are representative pharmaceutical compositions of the invention for topical use in lowering of intraocular pressure. Each of formulations A through E may be formulated in accordance with procedures known to those skilled in the art.

## FORMULATION A

Ingredient	Amount (wt%)
Compound of formula II	0.003
Dextran 70	0.1
Hydroxypropyl methylcellulose	0.3
Sodium Chloride	0.77
Potassium chloride	0.12
Disodium EDTA (Edetate disodium)	0.05
Benzalkonium chloride	0.01
HCl and/or NaOH	pH 7.2 - 7.5
Purified water	q.s. to 100%

## FORMULATION B

Ingredient	Amount (wt%)
Compound of formula III	0.001
Monobasic sodium phosphate	0.05
Dibasic sodium phosphate (anhydrous)	0.15
Sodium chloride	0.75
Disodium EDTA (Edetate disodium)	0.01
Benzalkonium chloride	0.02
Polysorbate 80	0.15
HCl and/or NaOH	pH 7.3 - 7.4
Purified water	q.s. to 100%

## FORMULATION C

Ingredient	Amount (wt%)
Compound of formula III	0.001
Dextran 70	0.1
Hydroxypropyl methylcellulose	0.5
Monobasic sodium phosphate	0.05
Dibasic sodium phosphate (anhydrous)	0.15
Sodium chloride	0.75
Disodium EDTA (Edetate disodium)	0.05
Benzalkonium chloride	0.01
NaOH and/or HCl	pH 7.3 - 7.4
Purified water	q.s. to 100%



## FORMULATION D

Ingredient	Amount (wt%)
Compound of formula II	0.003
Monobasic sodium phosphate	0.05
Dibasic sodium phosphate (anhydrous)	0.15
Sodium chloride	0.75
Disodium EDTA (Edetate disodium)	0.05
Benzalkonium chloride	0.01
HCl and/or NaOH	pH 7.3 - 7.4
Purified water	q.s. to 100%

## FORMULATION E

Ingredient	Amount (wt/vol%)
Compound of formula II	0.01
Polyoxyl 35 castor oil	0.1
Tromethamine	0.12
Boric acid	0.3
Mannitol	4.6
Disodium EDTA (edetate disodium)	0.1
Benzalkonium Chloride Solution	0.01
HCl and/or NaOH	pH 7.3 - 7.4
Purified Water	q.s. to 100%

EXAMPLE 3

In the present study compounds II and III, and PGF<sub>2</sub> $\alpha$  isopropyl ester (PGF<sub>2</sub> $\alpha$ iPr) were tested for ocular irritation in the New Zealand (NZA) rabbit. Prostaglandins were dosed as 1.0 microgram of compound per treatment in 30  $\mu$ L of test formulation. Conjunctival hyperemia, swelling and discharge were evaluated using a system devised to grossly compare the irritation potential of prostaglandins in the NZA rabbit. Using the Hackett/McDonald scoring system (Hackett, R.B. and McDonald, T.O. "Eye Irritation" in Dermatotoxicology, 4th edition, Marzulli, F.N. and Maibach, H.I. editors, Hemisphere Publishing Corp., Washington D.C. (1991)), conjunctival hyperemia, conjunctival swelling, and ocular discharge were graded using a slit-lamp prior to compound instillation and 1, 2, 3, and 5 hours after topical ocular instillation of the test compounds. The percentage of eyes scoring +2 or greater for all time points was calculated for each parameter (conjunctival hyperemia, conjunctival swelling, and ocular discharge). To facilitate comparison, PGF<sub>2</sub> $\alpha$ iPr was administered at the same time as the test agent. The cumulative results are presented in Table 1.

Table 1:

Compound	Number of Animals	% Incidence		
		Hyperemia	Conjunctival Swelling	Discharge
II	10	0	0	5
PGF <sub>2</sub> $\alpha$ iPr	8	69	59	69
III	10	0	0	0
PGF <sub>2</sub> $\alpha$ iPr	10	48	18	13

5

Discussion:

It is evident from Table 1 that the conformationally rigid analogs of PGF<sub>2</sub> $\alpha$  isopropyl ester, compounds II and III, produced a low incidence of ocular irritation in the rabbit compared to PGF<sub>2</sub> $\alpha$  isopropyl ester, which caused a relatively high incidence of hyperemia, conjunctival swelling and discharge. This indicates that the structural modification present in compounds II and III attenuates the ocular side effects associated with the PGF<sub>2</sub> $\alpha$  isopropyl ester.

EXAMPLE 4

In the study presented below, compounds II and III, and PGF<sub>2</sub>α isopropyl ester (PGF<sub>2</sub>α iPr) were tested for IOP-lowering effect in cynomologus monkey eyes. The right eyes of the cynomologus monkeys in this study were previously given laser trabeculoplasty to induce ocular hypertension in the lasered eye. Animals had been trained to sit in restraint chairs and conditioned to accept experimental procedures without chemical restraint. IOP was determined with a pneumatonometer after light corneal anesthesia with dilute proparacaine. The test protocol included a five-dose b.i.d. treatment regimen because of the typical delayed response to prostaglandins. The test formulations were administered to the lasered right eyes, and the normal left eyes remained untreated for compounds II and III, or to both eyes for PGF<sub>2</sub>α isopropyl ester (PGF<sub>2</sub>α iPr).

Baseline IOP values were determined prior to treatment with the test formulation, and IOP was determined 16 hours after the fourth dose for all compounds, 2, 4, and 6 hours after the fifth dose for compounds II and III, and 1, 3 and 7 hours after the fifth dose for PGF<sub>2</sub>α iPr. Results are presented in Table 2 as the mean percent reduction of IOP from baseline +/- SEM. Prostaglandins were dosed as 1.0 microgram of compound per treatment in 30 μL of test formulation.

Table 2:

Compound	Number of Animals	Baseline IOP (mm Hg)	Percent IOP Reduction +/- SEM (Hours after Last Dose/Dose #)						
			16/4	1/5	2/5	3/5	4/5	6/5	7/5
II	9	37.9	20.9+/-4.1		16.3+/-5.1		24.2+/-5.8	27.4+/-5.9	
III	9	43.7	11.4+/-4.0		20.3+/-4.6		24+/-4.5	15+/-5.0	
PGF <sub>2</sub> α iPr	4	34.8	5.8+/-4.0	27.6+/-14.4		38+/-11.7			25.6+/-14.4

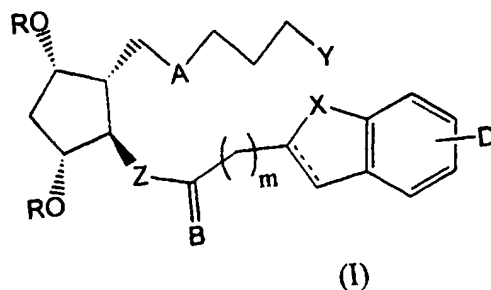
Discussion:

Table 2 shows that the conformationally rigid analogs of PGF<sub>2</sub> $\alpha$  isopropyl ester, compounds II and III, produce a significant degree of IOP reduction for the time period  
5 tested. Thus, the conformationally rigid compounds II and III, with their low incidence of side effects (Example 3), exhibit a significantly improved therapeutic profile over PGF<sub>2</sub> $\alpha$  isopropyl ester.

The invention has been described by reference to certain preferred embodiments  
10 however, it should be understood that it may be embodied in other specific forms or variations thereof without departing from its spirit or essential characteristics. The embodiments described above are therefore considered to be illustrative in all respects and not restrictive, the scope of the invention being indicated by the appended claims rather than by the foregoing description.

What is claimed is:

1. A method of treating glaucoma and ocular hypertension which comprises topically administering to the affected eye a therapeutically effective amount of a compound of formula (I).



wherein:

$Y = C(O)NR_1R_2$ ,  $CH_2OR_3$ ,  $CH_2NR_2$ ,  $CO_2R_1$ , or  $CO_2M$ , where M is a cationic salt moiety;

$R_1$ ,  $R_2$  (same or different) = H,  $C_1$ - $C_6$  alkyl or alkenyl, or  $C_3$ - $C_6$  cycloalkyl;

$R$ ,  $R_3$  (same or different) =  $C(O)R_4$  or H, where  $R_4$  =  $C_1$ - $C_6$  alkyl or alkenyl, or  $C_3$ - $C_6$  cycloalkyl;

$A = CH_2CH_2$ , *cis* or *trans*  $CH=CH$ , or  $C\equiv C$ ;

$Z = CH_2CH_2$  or *trans*  $CH=CH$ ;

$X = O$ ,  $S(O)_n$ ,  $(CH_2)_n$ , where  $n = 0, 1$ , or  $2$ ;

$B = H$  and  $OH$  in either configuration or double bonded  $O$ ;

$D = R_1$ ,  $OR_1$ , halogen,  $S(O)_nR_4$ ,  $NO_2$ ,  $NR_1R_2$ , H, or  $CF_3$ , where  $n = 0, 1$ , or  $2$ , and  $R_1$ ,  $R_2$  and

$R_4$  are as defined above; and

$m = 0, 1$ , or  $2$ .

2. The method of claim 1, wherein:  $Y = CO_2R_1$ , where  $R_1 = H$ ,  $C_1$ - $C_6$  alkyl or alkenyl, or  $C_3$ - $C_6$  cycloalkyl;  $R = C(O)R_4$  or  $H$ , where  $R_4 = C_1$ - $C_6$  alkyl or alkenyl, or  $C_3$ - $C_6$  cycloalkyl;  $A = CH_2CH_2$ , *cis* or *trans*  $CH=CH$ , or  $C\equiv C$ ;  $Z = CH_2CH_2$  or *trans*  $CH=CH$ ;  $X = O$  or  $CH_2$ ;  $B = H$  and  $OH$  in either configuration; and  $D = R_1$ ,  $OR_1$ , halogen, or  $H$ , where  $R_1$  is as defined above.

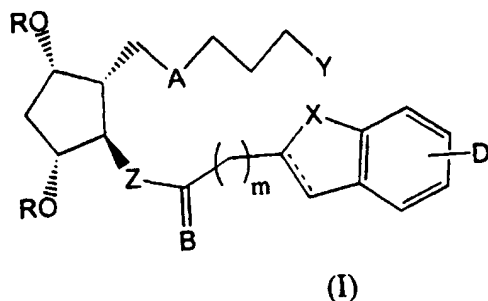
3. The method of claim 2, wherein:  $Y = CO_2R_1$ , where  $R_1 = C_3$  alkyl in the isopropyl form;  $R = H$ ;  $A = CH_2CH_2$  or *cis*  $CH=CH$ ;  $Z = CH_2CH_2$  or *trans*  $CH=CH$ ;  $X = CH_2$ ;  $B = \beta$ -H and  $\alpha$ -OH; and  $D = H$ .

4. The method of claim 1, wherein between about 0.01 and about 1000 micrograms of the compound is administered.

5. The method of claim 4, wherein between about 0.1 and about 100 micrograms of the compound is administered.



6. A topical ophthalmic composition for the treatment of glaucoma and ocular hypertension, said composition comprising an ophthalmically acceptable vehicle and a therapeutically effective amount of a compound of formula (I):



wherein:

$Y = C(O)NR_1R_2$ ,  $CH_2OR_3$ ,  $CH_2NR_2$ ,  $R_2$ ,  $CO_2R_1$ , or  $CO_2M$ , where  $M$  is a cationic salt moiety;

$R_1$ ,  $R_2$  (same or different) = H,  $C_1$ - $C_6$  alkyl or alkenyl, or  $C_3$ - $C_6$  cycloalkyl;

$R$ ,  $R_3$  (same or different) =  $C(O)R_4$  or H, where  $R_4 = C_1$ - $C_6$  alkyl or alkenyl, or  $C_3$ - $C_6$  cycloalkyl;

$A = CH_2CH_2$ , *cis* or *trans*  $CH=CH$ , or  $C\equiv C$ ;

$Z = CH_2CH_2$ , or *trans*  $CH=CH$ ;

$X = O$ ,  $S(O)_n$ , or  $(CH_2)_n$ , where  $n = 0, 1$  or  $2$ ;

$B = H$  and  $OH$  in either configuration or double bonded  $O$ ;

$D = R_1$ ,  $OR_1$ , halogen,  $S(O)_nR_4$ ,  $NO_2$ ,  $NR_1R_2$ , H, or  $CF_3$ , where  $n = 0, 1$ , or  $2$ , and  $R_1$ ,  $R_2$  and  $R_4$  are as defined above; and

$m = 0, 1$ , or  $2$ .

7. The composition of claim 6, wherein:  $Y = CO_2R_1$ , where  $R_1 = H$ ,  $C_1$ - $C_6$  alkyl or alkenyl, or  $C_3$ - $C_6$  cycloalkyl;  $R = C(O)R_4$  or  $H$ , where  $R_4 = C_1$ - $C_6$  alkyl or alkenyl, or  $C_3$ - $C_6$  cycloalkyl;  $A = CH_2CH_2$ , *cis* or *trans*  $CH=CH$ , or  $C\equiv C$ ;  $Z = CH_2CH_2$ , or *trans*  $CH=CH$ ;  $X = O$  or  $(CH_2)_n$ , where  $n = 1$  or  $2$ ;  $B = H$  and  $OH$  in either configuration; and  $D = R_1$ ,  $OR_1$ , halogen, or  $H$ , where  $R_1$  is as defined above.

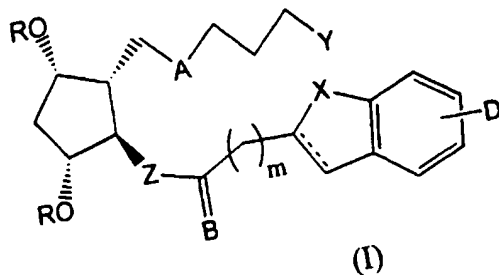
8. The composition of claim 7, wherein:  $Y = CO_2R_1$ , where  $R_1 = C_3$  alkyl in the isopropyl form;  $R = H$ ;  $A = CH_2CH_2$  or *cis*  $CH=CH$ ;  $Z = CH_2CH_2$  or *trans*  $CH=CH$ ;  $X = O$  or  $CH_2$ ;  $B = \beta$ -H and  $\alpha$ -OH; and  $D = H$ .

9. The composition of claim 8, wherein  $Z = CH_2CH_2$ .

10. The composition of claim 6, wherein the compound is present at a concentration between about 0.0001 and about 5 percent by weight.

11. The composition of claim 9, wherein the compound is present at a concentration between about 0.001 and about 1 percent by weight.

12. A compound of formula I:



wherein:

Y = C(O)NR<sub>1</sub>R<sub>2</sub>, CH<sub>2</sub>OR<sub>3</sub>, CH<sub>2</sub>NR<sub>2</sub>, CO<sub>2</sub>R<sub>1</sub>, or CO<sub>2</sub>M, where M is a cationic salt moiety;

R<sub>1</sub>, R<sub>2</sub> (same or different) = H, C<sub>1</sub>-C<sub>6</sub> alkyl or alkenyl, or C<sub>3</sub>-C<sub>6</sub> cycloalkyl;

R, R<sub>3</sub> (same or different) = C(O)R<sub>4</sub> or H, where R<sub>4</sub> = C<sub>1</sub>-C<sub>6</sub> alkyl or alkenyl, or C<sub>3</sub>-C<sub>6</sub> cycloalkyl;

A = CH<sub>2</sub>CH<sub>2</sub>, *cis* or *trans* CH=CH, or C≡C;

Z = CH<sub>2</sub>CH<sub>2</sub>;

X = O, S(O)<sub>n</sub>, (CH<sub>2</sub>)<sub>n</sub>, where n = 0, 1, or 2;

B = H and OH in either configuration or double bonded O;

D = R<sub>1</sub>, OR<sub>1</sub>, halogen, S(O)<sub>n</sub>R<sub>4</sub>, NO<sub>2</sub>, NR<sub>1</sub>R<sub>2</sub>, H, or CF<sub>3</sub>, where n = 0, 1, or 2, and R<sub>1</sub>, R<sub>2</sub>, and

R<sub>4</sub> are as defined above; and

m = 0, 1, or 2.

13. The compound of claim 12, wherein X = CH<sub>2</sub> and A = CH<sub>2</sub>CH<sub>2</sub> or *cis* CH=CH.

# INTERNATIONAL SEARCH REPORT

Int. Application No.  
PCT/US 96/17901

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 C07C405/00 A61K31/557

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 152 527 A (HESS HANS-JUERGEN E ET AL) 1 May 1979 cited in the application see claims 1,31,38 ---	12,13
Y	WO 96 10407 A (ALCON LAB INC) 11 April 1996 * p.2, 1.13-18; claims 1-15 *	1-13
Y	WO 92 02496 A (KABI PHARMACIA AB) 20 February 1992 * p.1, 1st par.; Schemes 1 and 2 *	1-11
Y	EP 0 667 160 A (ALCON LAB INC) 16 August 1995 * p.2, 1.6-8 & 1.19-21; Table 1, cpd VII; claim 1 *	1-13
	-/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

16 July 1997

Date of mailing of the international search report

04.08.97

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040. Tx. 31 651 epo nl,

Authorized officer

Ilhan D

# INTERNATIONAL SEARCH REPORT

International Application No.  
PCT/US 96/17901

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	J MED CHEM, vol. 23, no. 5, 1980, pages 519-24, XP000655193 HAYASHI ET AL : "Prostaglandin analogues possessing...." cited in the application see table 1	12,13
	---	
Y	J MED CHEM, vol. 26, 1983, pages 328-34, XP000655248 SCHAFF ET AL: "Structure-activity of configurationally rigid arylprostaglandins" cited in the application see tables III,IV	12,13
	-----	

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PC1/US 96/17901

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4152527 A	01-05-79	AT 352754 B	10-10-79
		AT 345999 B	10-10-78
		AU 6230273 A	08-05-75
		BE 807046 A	08-05-74
		CA 1033727 A	27-06-78
		CA 1052781 A	17-04-79
		CA 1053669 A	01-05-79
		CH 593933 A	30-12-77
		CH 587283 A	29-04-77
		CH 593930 A	30-12-77
		DE 2355731 A	22-05-74
		DE 2365320 A	10-10-74
		FR 2205338 A	31-05-74
		FR 2286147 A	23-04-76
		FR 2291200 A	11-06-76
		GB 1456839 A	24-11-76
		GB 1456840 A	24-11-76
		GB 1456838 A	24-11-76
		IN 143298 A	29-10-77
		IN 142581 A	30-07-77
		IN 139265 A	29-05-76
		JP 1125139 C	30-11-82
		JP 49133357 A	21-12-74
		JP 57014347 B	24-03-82
		NL 7315307 A	10-05-74
		SE 412229 B	25-02-80
		SE 7612261 A	03-11-76
		SE 7612262 A	03-11-76
		SE 417957 B	27-04-81
		SE 7701523 A	10-02-77
		SU 667131 A	05-06-79
		SU 704456 A	15-12-79
		ZA 7308595 A	25-09-74
-----			
WO 9610407 A	11-04-96	AU 3639895 A	26-04-96
		EP 0783308 A	16-07-97
-----			
WO 9202496 A	20-02-92	AT 133162 T	15-02-96
		AU 645129 B	06-01-94
		AU 8391591 A	02-03-92

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCI/US 96/17901

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9202496 A		BG 61143 B CA 2067341 A DE 69116541 D DE 69116541 T EP 0495069 A JP 5502043 T US 5359095 A	31-12-96 09-02-92 29-02-96 19-09-96 22-07-92 15-04-93 25-10-94
EP 0667160 A	16-08-95	AU 7913894 A CA 2138181 A US 5627209 A	22-06-95 16-06-95 06-05-97